exist in the 20 to 25% of melanoma patients who express HLA-A3, In addition, immunotherapy directed against Pmel-17/ **gp100** and other shared melanoma Ags may be useful in a large subset of these patients.

3/3,AB/11 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07891085 EMBASE No: 1999364594
Murine dendritic cells transfected with human GP100 elicit both antigen-specific CD8sup + and CD4sup + T-cell responses and are more effective than DNA vaccines at generating anti-tumor immunity
Yang S.; Vervaert C.E.; Burch J. Jr.; Grichnik J.; Seigler H.F.; Darrow T.L.
T.L. Darrow, Department of Surgery, Box 3966, DUMC, Durham, NC 27710 United States
AUTHOR EMAIL: darro001@mc.duke.edu
International Journal of Cancer (INT. J. CANCER) (United States) 1999 , 83/4 (532-540)
CODEN: IJCNA ISSN: 0020-7136
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 22

Dendritic cells (DCs) are potent inducers of cytotoxic T lymphocytes (CTLs) when pulsed with an antigenic peptide or tumor lysate. In this report, we have used liposome-mediated gene transfer to examine the ability of plasmid DNA encoding the human melanoma-associated antigen **gp100** to elicit CD8sup + and CD4sup + T-cell responses. We also compared the efficacy between **gp100** gene-modified DCs and naked DNA (pCDNA3/ **gp100**)-based vaccines at inducing anti-tumor immunity. DCs were generated from murine bone marrow and transfected in vitro with plasmid DNA containing the **gp100** gene. These **gp100** - modified DCs (DC/gps) were used to stimulate syngeneic naive spleen T cells in vitro or to immunize mice in vivo. Antigen-specific, MHC-restricted CTLs were generated when DC/gps were used to prime T cells both in vitro and in vivo. Thus, these CTLs were cytolytic for **gp100** -transfected syngeneic (H-2sup b) tumor MCA106 (MCA/gp) and **vaccinia** -pMeII7/ **gp100** -infected syngeneic B16 and MCA106, but not parental tumor MCA106 and B16, or **gp100** -transfected allogeneic tumor P815 (H-2(d)). Immunization with DC/gp protected mice from subsequent challenge with MCA/gp but not parental MCA106. Antibody-mediated T-cell subset depletion experiments demonstrate that induction of CTLs in vivo is dependent on both CD4sup + and CD8sup + T cells. Furthermore, DC/gp immunization elicits an antigen-specific CD4sup + T-cell response, suggesting that DC/gps present MHC class II epitopes to CD4sup + T cells. In addition, our data show that gene-modified, DC-based vaccines are more effective than the naked DNA-based vaccines at eliciting anti-tumor immunity in both prophylactic and therapeutic models. These results suggest that the use of DCs transfected with plasmid DNA containing a gene for TAA may be superior to peptide-pulsed DCs and naked DNA-based vaccines for immunotherapy and could provide an alternative strategy for tumor vaccine design.

3/3,AB/12 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07632121 EMBASE No: 1999114502
Vaccination with a recombinant vaccinia virus encoding a 'self' antigen induces autoimmune vitiligo and tumor cell destruction in mice: Requirement for CD4sup + T lymphocytes
Overwijk W.W.; Lee D.S.; Surman D.R.; Irvine K.R.; Touloukian C.E.; Chan C.- C.; Carroll M.W.; Moss B.; Rosenberg S.A.; Restifo N.P.
N.P. Restifo, National Cancer Institute, Building 10, Bethesda, MD 20892-1502 United States
AUTHOR EMAIL: restifo@nih.gov
Proceedings of the National Academy of Sciences of the United States of

America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1999, 96/6 (2982-2987)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 48

Many human and mouse tumor antigens are normal, nonmutated tissue differentiation antigens. Consequently, immunization with these 'self' antigens could induce autoimmunity. When we tried to induce immune responses to five mouse melanocyte differentiation antigens, **gp100** , MART-1, tyrosinase, and tyrosinase-related proteins (TRP) 1 and TRP-2, we observed striking depigmentation and melanocyte destruction only in the skin of mice inoculated with a **vaccinia** virus encoding mouse TRP-1. These mice rejected a lethal challenge of B16 melanoma, indicating the immune response against TRP-1 could destroy both normal and malignant melanocytes. Cytotoxic T lymphocytes specific for TRP-1 could not be detected in depigmented mice, but high titers of IgG anti-TRP-1 antibodies were present. Experiments with knockout mice revealed an absolute dependence on major histocompatibility complex class II, but not major histocompatibility complex class I, for the induction of both vitiligo and tumor protection. Together, these results suggest that the deliberate induction of self-reactivity using a recombinant viral vector can lead to tumor destruction, and that in this model, CD4sup + T lymphocytes are an integral part of this process. Vaccine strategies targeting tissue differentiation antigens may be valuable in cancers arising from nonessential cells and organs such as melanocytes, prostate, testis, breast, and ovary.
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Targeted complementation of MHC class II deficiency by intrathymic delivery of recombinant adenoviruses.

AUTHOR: Rooke Ronald(a); Waltzinger Caroline; Benoist Christophe; Mathis Diane
AUTHOR ADDRESS: (a)Lab. Immunol., Inst. Recherches Clin. Montreal, 110 Ave. Pins Ouest, Montreal, PQ H2W 1R7**Canada
JOURNAL: Immunity 7 (1):p123-134 1997
ISSN: 1074-7613
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: De novo differentiation of CD4+ T cells was provoked in mice lacking major histocompatibility complex (MHC) class II molecules by intrathymic injection of adenovirus vectors carrying class II genes. This permits a new approach to questions concerning the dynamics of CD4+ T cell compartments in the thymus and peripheral lymphoid organs. Here two issues are explored. First, we show that mature CD4+CD8- cells reside in the thymus for a protracted period before emigrating to the periphery, highlighting the potential importance of, and our ignorance of, the postselection maturation period. Second, we demonstrate that the survival of CD4+ cells in peripheral lymphoid organs is markedly curtailed when class II molecules are absent and is not further reduced in the absence of both class II and class I molecules, raising the possibility that MHC-mediated selection may continue in the periphery.

1997

Intranodal immunization with tumor lysate-pulsed dendritic cells enhances protective antitumor immunity.

Lambert LA; Gibson GR; Maloney M; Durell B; Noelle RJ; Barth RJ

Department of Surgery, Dartmouth Medical School and Norris Cotton Cancer Center, Lebanon, New Hampshire 03756, USA.

Cancer research (United States) Jan 15 2001, 61 (2) p641-6, ISSN 0008-5472 Journal Code: CNF

Contract/Grant No.: 1R29CA776612-01, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We developed a technique for direct inguinal lymph node injection in mice to compare various routes of immunization with tumor lysate-pulsed dendritic cell (DC) vaccines. Syngeneic, bone marrow-derived, tumor lysate-pulsed DCs administered intranodally generated more potent protective antitumor immunity than s.c. or i.v. DC immunizations. Intranodal immunization with ovalbumin peptide-pulsed DCs induced significantly greater antigen-specific T-lymphocyte expansion in the spleen than either s.c. or i.v. immunization. Furthermore, a significantly more potent, antigen-specific TH1-type response to the ovalbumin peptide was induced by intranodal, compared with s.c. or i.v., immunization. Intranodal immunization, designed to enhance DC-T cell interaction in a lymphoid environment, optimizes induction of T lymphocyte-mediated protective antitumor immunity. These results support the use of intranodal immunization as a feasible and effective route of DC vaccine administration.

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ds

Set     Items   Description
S1         58   GP100 (S) (VACCINIA OR ALVAC OR NYVAC)
S2         16   RD (unique items)
S3         12   S2 NOT PY>1999
S4         53   (CEA OR MAGE) (S) (ALVAC)
S5         17   RD (unique items)
S6          9   S5 NOT PY>1999
S7         20   (IMEQVPFSY OR YLEPGPVTV OR YLSGADLNL)
S8          4   RD (unique items)
S9       1295   INTRANODAL?
S10         0   S9 AND (VACCINIA OR ALVAC)
S11        11   S9 AND (VECTOR? OR PLASMID? OR CONSTRUCT? OR RETROVIR? OR -
              ADENOVIR?)
S12         9   RD (unique items)
S13      3826   (NODE OR NODES OR INTRANODALLY) (S) (VECTOR? OR PLASMID? OR
              RETROVIR? OR ADENOVIR? OR VACCINIA OR POXVIRUS OR ALVAC)
S14       666   S13 AND (INJECT?)
S15       367   S14 AND (ANTIGEN? OR IMMUNIZ? OR VACCIN?)
S16         0   S15 AND INTRANODALLY
S17        23   INTRANODALLY
S18        10   RD (unique items)
?
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Identification of five MAGE-A1 epitopes recognized by cytolytic T lymphocytes obtained by in vitro stimulation with dendritic cells transduced with MAGE-A1.

Chaux P; Luiten R; Demotte N; Vantomme V; Stroobant V; Traversari C; Russo V; Schultz E; Cornelis GR; Boon T; van der Bruggen P

Ludwig Institute for Cancer Research, Brussels, Belgium.

Journal of immunology (UNITED STATES) Sep 1 1999, 163 (5) p2928-36, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

MAGE genes are expressed by many human tumors of different histological types but not by normal cells, except for male germline cells. The Ags encoded by **MAGE** genes and recognized by T cells are therefore strictly tumor-specific. Clinical trials involving therapeutic vaccination of cancer patients with **MAGE** antigenic peptides or proteins are in progress. To increase the range of patients eligible for therapy with peptides, it is important to identify additional **MAGE** epitopes recognized by CTL. Candidate peptides known to bind to a given HLA have been used to stimulate T lymphocytes in vitro. In some instances, CTL clones directed against these synthetic peptides have been obtained, but these clones often failed to recognize tumor cells expressing the relevant gene. Therefore, we designed a method to identify CTL epitopes that selects naturally processed peptides. Monocyte-derived dendritic cells infected with a recombinant canarypoxvirus (**ALVAC**) containing the entire **MAGE** -A1 gene were used to stimulate CD8+ T lymphocytes from the blood of individuals without cancer. Responder cell microcultures that specifically lysed autologous cells expressing **MAGE** -A1 were cloned using autologous stimulator cells either transduced with a retrovirus coding for **MAGE** -A1 or infected with recombinant Yersinia- **MAGE** -A1 bacteria. The CTL clones were tested for their ability to lyse autologous cells loaded with each of a set of overlapping **MAGE** -A1 peptides. This strategy led to the identification of five new **MAGE** -A1 epitopes recognized by CTL clones on HLA-A3, -A28, -B53, -Cw2, and -Cw3 molecules. All of these CTL clones recognized target cells expressing gene **MAGE** -A1.

6/3,AB/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10239208 99385433 PMID: 10458251

Phase I study in cancer patients of a replication-defective avipox recombinant vaccine that expresses human carcinoembryonic antigen.

Marshall JL; Hawkins MJ; Tsang KY; Richmond E; Pedicano JE; Zhu MZ; Schlom J

Georgetown University Medical Center, Vincent T. Lombardi Cancer Center, Washington, DC 20007, USA.

Journal of clinical oncology (UNITED STATES) Jan 1999, 17 (1) p332-7, ISSN 0732-183X Journal Code: JCO

Contract/Grant No.: 2 P30 CA51008, CA, NCI; U01 CA62500, CA, NCI

Languages: ENGLISH

Document type: Clinical Trial; Clinical Trial, Phase I; Journal Article

Record type: Completed

PURPOSE: A phase I clinical trial in patients with advanced carcinoma was conducted, using a replication-defective avipox vaccine containing the gene for the human carcinoembryonic antigen (**CEA**). The canarypox vector, designated **ALVAC** , has the ability to infect human cells but cannot replicate. PATIENTS AND METHODS: The recombinant vaccine, designated **ALVAC** - **CEA** , was administered intramuscularly three times at 28-day intervals. Each cohort of six patients received three doses of either 2.5 x 10(5), 2.5 x 10(6), or 2.5 x 10(7) plaque-forming units of vaccine. RESULTS: The vaccine was well tolerated at all dose levels and no significant toxicity was attributed to the treatment. No objective antitumor response was observed during the trial in patients with measurable disease. Studies were conducted to assess whether **ALVAC** - **CEA** had the ability to induce cytolytic T-lymphocyte (CTL) responses in patients with advanced cancer. Peripheral blood mononuclear cells (PBMCs) from patients with the MHC class I A2 allele were obtained before vaccine administration and 1 month after the third vaccination. Peripheral blood mononuclear cells were incubated

CEA -specific immunity is being assessed by ELISPOT assay using peripheral T-lymphocytes derived from patients before and after immunization. **ALVAC - CEA** -B7.1 vaccine therapy is safe in metastatic cancer patients at doses up to 4.5 x 10e8 PFU. Although we did not find durable clinical responses, there was some evidence of disease stabilization. If we can confirm evidence for **CEA** recognition by ELISPOT further clinical trials with this vaccine may be warranted.

6/3,AB/6 (Item 2 from file: 159)
DIALOG(R)File 159:Cancerlit

01590608 99701682
Phase I/II Trial of Vaccinia- Cea **(V) and** Alvac **- Cea (A) in Patients with Advanced** Cea **-Bearing Tumors. (Meeting abstract).**
Marshall John; Richmond Elle; Pedicano James; Tsang Alfre; Arlen Phili; Schlom Jeffre
Laboratory of Tumor Immunology and Biology NCI, Bethesda, MD.
Proc Annu Meet Am Soc Clin Oncol; 18 1999
Languages: ENGLISH
Document Type: MEETING ABSTRACTS
Record type: Completed
In previous clinical trials, we and others have documented the safety and immunologic impact of 2 CEA-targeting vaccines given alone to patients with advanced cancer. V was found to be a potent immunogen but of little additional benefit following repeated injections. A was less potent but increases in T cell responses were seen with each subsequent injection. Preclinical studies have shown the potentiation of antitumor activity by the combination of these 2 compounds. Conflicting data existed concerning the order of administration which would result in the best immunologic response. To explore this 'prime and boost' question in clinical trials, we randomized 18 patients with advanced or high risk CEA-bearing tumors to receive either V-A-A-A or A-A-A-V, with vaccinations given every 28 days. 6 HLA A-2 positive patients were enrolled on each arm for immunologic monitoring purposes. Patients were followed for evidence of antitumor activity (when possible), toxicity, and changes in the precursor frequencies (PF) of cytoxic T cells specific to the CEA peptide CAP1-6D as measured by ELISPOT. No objective antitumor responses were seen. No treatment-related toxicity was seen except for minor skin reactions at vaccination sites. All 6 patients treated with V-A-A-A developed significant increases in CAP1-6D T cell PF whereas only 2 of 5 evaluable patients who received A-A-A-V showed increased T cell PF. Reasons for this difference are unclear. Patients are currently being accrued to V-A-A-A +GM-CSF +/- IL-2 to determine the impact of these cytokines on clinical and immunologic end points. Supported by R03 CA81378-01

6/3,AB/7 (Item 3 from file: 159)
DIALOG(R)File 159:Cancerlit

01590604 99701678
Phase I Trial with ALVAC **- CEA B7.1 Immunization in Advanced** CEA **-Expressing Adenocarcinomas (Meeting abstract).**
Mehren M Vo; Davey M; Rivera V; Yeslow G; Gillon T; Alpaugh K; Cheng J; Meropol N; Rosvold E; Scher R; Cooper H; Schlom J; Weiner LM
Departments of Medical Oncology and Pathology, Fox Chase Cancer Center, Philadelphia, PA, and Laboratory of Tumor Immunology and Biology, National Cancer Institute, Bethesda, MD.
Proc Annu Meet Am Soc Clin Oncol; 18 1999
Languages: ENGLISH
Document Type: MEETING ABSTRACTS
Record type: Completed
Preclinical studies have shown immunization to antigens is enhanced in the presence of the B7.1 costimulatory molecule. The novel recombinant vaccine, **ALVAC - CEA** B7.1, is a canary pox virus modified to contain the genes for **CEA** and B7.1. Thirty-nine patients with advanced **CEA** -expressing adenocarcinomas (colorectal n = 28, breast n = 3, pancreas n =

2, and lung, thyroid, appendix, gallbladder n = 1) have been immunized intradermally every other week [times] 4; patients with stable or responding disease receive monthly boosts until progression. Doses evaluated were 2.5 [times] 10[Superscript 7] pfu (n = 3), 1.0 [times] 10[Superscript 8] (n = 6), and 4.5 [times] 10[Superscript 8] pfu (n = 30). All patients have erythema and swelling at vaccine sites. Grade 3--4 toxicities due to therapy are fatigue, fever, and myalgiase seen in a minority of patients for 24--48 hours post vaccine. Vaccine site biopsies from patients treated with 4.5 [times] 10[Superscript 8] pfu were done 48 hours post injection. All biopsy specimens to date (n = 26) have demonstrated leukocytic infiltrates in perivascular regions. Infiltrates in the dermis and underlying fat were observed in 15 patients, and necrosis in 2 samples. Immunohistochemistry using a polyclonal **CEA** antibody has demonstrated **CEA** staining of leukocytic infiltrates (n = 24), endothelial cells (n = 5) and spindle shaped cells suggestive of dendritic cells (n = 6). Six of 28 evaluable patients had disease stabilization after 4 vaccinations. Two patients had disease progression after 2 booster injections, while 4 continue on study, having received 1--4 booster injections. Six of twenty-one patients with elevated pretreatment serum **CEA** levels have had decreases lasting 4--13 weeks (mean % of baseline = 34%); 4 of these have had stabilization of disease. Evaluation of humoral responses to **CEA** , **ALVAC** and B7.1 are being examined. T-cell responses to an HLA-A2 specific **CEA** peptide also are being performed in HLA A-2 positive patients (n = 26) by ELISPOT assay evaluating IFN<FONT>g production. This study will accrue another 30 patients to be treated with adjuvant GM-CSF days -3 to +2 with 4.5 [times] 10[Superscript 8] pfu **ALVAC** - **CEA** B7.1. Immunization with **ALVAC** - **CEA** B7.1 can be achieved with minimal toxicity with evidence for **CEA** transduction and disease stabilization in some patients.

6/3,AB/8 (Item 4 from file: 159)

01221045 95609272

Generation of antigen-specific cytotoxic T-cells in breast cancer by in vitro stimulation of human tumor infiltrating lymphocytes with a recombinant avipox-MAGE-1 virus (Meeting abstract).

Oshidari F; Talib S; Lebkowski J; Tartaglia J; Weinhold K; Toso J
Applied Immune Sciences, Inc., Santa Clara, CA 95054

Proc Annu Meet Am Assoc Cancer Res; 36 1995 ISSN 0197-016X
Languages: ENGLISH
Document Type: MEETING ABSTRACTS
Record type: Completed

Tumor associated antigens are potential targets for active immunotherapy. **MAGE** -1, a non-mutated gene, is not usually expressed in normal cells, but is detected in melanoma and breast carcinoma. Because of its relatively high frequency of expression in various tumors and its proven immunogenicity, **MAGE** -1 represents a potential target for developing tumor-specific immunotherapy. We have utilized a recently developed recombinant avipox vector (**ALVAC**) containing the **MAGE** -1 gene to induce tumor-specific CTL from a breast cancer patient. TIL obtained from the breast tumor were in vitro stimulated with irradiated autologous PBL acutely infected with the **ALVAC** - **MAGE** -1 recombinant. The TIL preferentially expanded and specifically recognized an allogeneic transformed B-cell line either pulsed with MZ2-E nonapeptide or infected with a vaccinia **MAGE** -1 recombinant in the context of HLA-A2 and/or B7. To further investigate the clonality of the in vitro expanded T-cells we analyzed T-cell receptor (TCR) V gene usage. TCR Vbeta analysis by quantitative multiprobe RNase protection assay showed preferential expansion of TCR Vbeta6.3 and Vbeta6.4. No such bias was present in the PBL of the patient. These results suggest that tumor-antigen-specific, MHC restricted CTL may be generated from the TIL of HLA-A1 breast cancer patients by in vitro stimulation with a recombinant avipox **MAGE** -1 virus. Thus, HLA-A1 patients bearing **MAGE** -1 tumors may benefit from **ALVAC** - **MAGE** -1 immunotherapy.

6/3,AB/9 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11929101 BIOSIS NO.: 199900175210
Specific T-cell responses to human carcinoembryonic antigen from patients immunized with recombinant canarypox (ALVAC)- CEA vaccine.
AUTHOR: Zhu M Z(a); Marshall J; Cole D; Lam C; Terasawa H(a); Schlom J(a); Tsang K Y(a)
AUTHOR ADDRESS: (a)NCI/NIH, Bethesda, MD 20892**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p423 March, 1999
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999
?

8/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10517935 20175479 PMID: 10709104

Agonist peptide from a cytotoxic t-lymphocyte epitope of human carcinoembryonic antigen stimulates production of tc1-type cytokines and increases tyrosine phosphorylation more efficiently than cognate peptide.

Salazar E; Zaremba S; Arlen PM; Tsang KY; Schlom J

Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-1750, USA.

International journal of cancer. Journal international du cancer (UNITED STATES) Mar 15 2000, 85 (6) p829-38, ISSN 0020-7136 Journal Code: GQU

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The identification of an agonist peptide (**YLSGADLNL** , designated CAP1-6D) to an immunodominant cytotoxic T-lymphocyte (CTL) epitope (designated CAP1) of human carcinoembryonic antigen (CEA) has previously been reported. The agonist peptide harbors a single amino acid substitution at a non-MHC anchor residue and is proposed to exert its effects at the level of the T-cell receptor (TCR). The type and magnitude of cytokines produced by CAP1-reactive CTL upon stimulation with the agonist peptide, CAP1-6D, were compared to those obtained upon stimulation with the cognate CAP1 peptide. In addition, early events in the TCR signaling pathway were examined for differences in tyrosine phosphorylation. Upon stimulation with the agonist peptide CAP1-6D, several different CEA-specific CTL lines exhibited a marked shift in the peptide dose response, which resulted in as much as a 1,000-fold increase in the levels of GM-CSF and gamma-IFN produced as compared with the use of the CAP1 peptide. However, levels of IL-4 and IL-10, which are associated with anti-inflammatory effects, were very low or non-existent. The cytokine profile of CAP1- and CAP1-6D-specific CTL is consistent with a Tc1-type CTL. Consistent with these findings, CEA-specific CTL showed increased tyrosine phosphorylation of TCR signaling proteins ZAP-70 and TCR zeta chains in response to both peptides. However, when CAP1-6D was compared with the wild-type peptide, the increase in ZAP-70 phosphorylation was greater than the increase in zeta phosphorylation. CTL generated with the CAP1-6D agonist were shown capable of lysis of human carcinoma cells expressing native CEA. The ability to upregulate the production of GM-CSF, gamma-IFN, TNFalpha and IL-2 with the agonist peptide, as compared with CAP1, may help in initiating or sustaining anti-tumor immune responses and thus potentially prove to be useful in the treatment of CEA-positive tumors. Copyright 2000 Wiley-Liss, Inc.

8/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09966415 99035510 PMID: 9815296

Immunization of patients with melanoma peptide vaccines: immunologic assessment using the ELISPOT assay.

Pass HA; Schwarz SL; Wunderlich JR; Rosenberg SA

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

cancer journal from Scientific American (UNITED STATES) Sep-Oct 1998, 4 (5) p316-23, ISSN 1081-4442 Journal Code: CR8

Comment in Cancer J Sci Am. 1998 Sep-Oct;4(5) 298-9

Languages: ENGLISH

Document type: Clinical Trial; Journal Article

Record type: Completed

PURPOSE: Interest in the development of antimelanoma peptide vaccines has been renewed by the identification of specific epitopes recognized by tumor-infiltrating lymphocytes that mediate tumor regression after adoptive transfer. The human leukocyte antigen (HLA)-A2*0201-restricted, nonmutated melanocyte differentiation antigen gp100 has multiple T-cell epitopes, of which three are recognized by most gp100-reactive tumor infiltrating lymphocytes. Synthetic peptides based on two of these epitopes, or modifications to improve HLA binding affinity, were used individually to

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            414  ALVAC
            197  NYVAC
      S1     58  GP100 (S) (VACCINIA OR ALVAC OR NYVAC)
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...examined 50 records  (50)
...completed examining records
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             16  S2
        4609164  PY>1999
      S3     12  S2 NOT PY>1999
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 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10364496   99438136   PMID: 10508491
  Murine  dendritic  cells  transfected  with  human  GP100  elicit  both
antigen-specific  CD8(+) and CD4(+) T-cell responses and are more effective
```

than DNA vaccines at generating anti-tumor immunity.

Yang S; Vervaert CE; Burch J; Grichnik J; Seigler HF; Darrow TL

Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA.

International journal of cancer. Journal international du cancer (UNITED STATES) Nov 12 1999, 83 (4) p532-40, ISSN 0020-7136 Journal Code: GQU

Contract/Grant No.: R01-CA64949, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Dendritic cells (DCs) are potent inducers of cytotoxic T lymphocytes (CTLs) when pulsed with an antigenic peptide or tumor lysate. In this report, we have used liposome-mediated gene transfer to examine the ability of plasmid DNA encoding the human melanoma-associated antigen **gp100** to elicit CD8(+) and CD4(+) T-cell responses. We also compared the efficacy between **gp100** gene-modified DCs and naked DNA (pCDNA3/ **gp100**)-based vaccines at inducing anti-tumor immunity. DCs were generated from murine bone marrow and transfected in vitro with plasmid DNA containing the **gp100** gene. These **gp100** -modified DCs (DC/gps) were used to stimulate syngeneic naive spleen T cells in vitro or to immunize mice in vivo. Antigen-specific, MHC-restricted CTLs were generated when DC/gps were used to prime T cells both in vitro and in vivo. Thus, these CTLs were cytolytic for **gp100** -transfected syngeneic (H-2(b)) tumor MCA106 (MCA/gp) and **vaccinia** -pMel17/ **gp100** -infected syngeneic B16 and MCA106, but not parental tumor MCA106 and B16, or **gp100** -transfected allogeneic tumor P815 (H-2(d)). Immunization with DC/gp protected mice from subsequent challenge with MCA/gp but not parental MCA106. Antibody-mediated T-cell subset depletion experiments demonstrate that induction of CTLs in vivo is dependent on both CD4(+) and CD8(+) T cells. Furthermore, DC/gp immunization elicits an antigen-specific CD4(+) T-cell response, suggesting that DC/gps present MHC class II epitopes to CD4(+) T cells. In addition, our data show that gene-modified, DC-based vaccines are more effective than the naked DNA-based vaccines at eliciting anti-tumor immunity in both prophylactic and therapeutic models. These results suggest that the use of DCs transfected with plasmid DNA containing a gene for TAA may be superior to peptide-pulsed DCs and naked DNA-based vaccines for immunotherapy and could provide an alternative strategy for tumor vaccine design. Copyright 1999 Wiley-Liss, Inc.

3/3,AB/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10298762 98158511 PMID: 9498746

Human melanoma patients recognize an HLA-A1-restricted CTL epitope from tyrosinase containing two cysteine residues: implications for tumor vaccine development.

Kittlesen DJ; Thompson LW; Gulden PH; Skipper JC; Colella TA; Shabanowitz J; Hunt DF; Engelhard VH; Slingluff CL; Shabanowitz JA

Department of Surgery, The Beirne Carter Center for Immunology, University of Virginia, Charlottesville 22908, USA.

Journal of immunology (UNITED STATES) Mar 1 1998, 160 (5) p2099-106, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI20963, AI, NIAID; AI21393, AI, NIAID; CA57653, CA, NCI; +

Erratum in J Immunol 1999 Mar 1;162(5) 3106; Erratum in Note Shabanowitz JA[corrected to Shabanowitz J]

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

To identify shared epitopes for melanoma-reactive CTL restricted by MHC molecules other than HLA-A*0201, six human melanoma patient CTL lines expressing HLA-A1 were screened for reactivity against the melanocyte differentiation proteins Pmel-17/ **gp100** , MART-1/Melan-A, and tyrosinase, expressed via recombinant **vaccinia** virus vectors. CTL from five of the six patients recognized epitopes from tyrosinase, and recognition of HLA-A1+ target cells was strongly correlated with tyrosinase expression. Restriction by HLA-A1 was further demonstrated for two of those

tyrosinase-reactive CTL lines. Screening of 119 synthetic tyrosinase peptides with the HLA-A1 binding motif demonstrated that nonamer, decamer, and dodecamer peptides containing the sequence KCDICTDEY (residues 243-251) all reconstituted the CTL epitope in vitro. Epitope reconstitution in vitro required high concentrations of these peptides, which was hypothesized to be a result of spontaneous modification of cysteine residues, interfering with MHC binding. Substitution of serine or alanine for the more N-terminal cysteine prevented modification at that residue and permitted target cell sensitization at peptide concentrations 2 to 3 orders of magnitude lower than that required for the wild-type peptide. Because spontaneous modification of sulfhydryl groups may also occur in vivo, tumor vaccines using this or other cysteine-containing peptides may be improved by amino acid substitutions at cysteine residues.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10163677 99290636 PMID: 10363968
Recombinant virus vaccination against "self" antigens using anchor-fixed immunogens.
Irvine KR; Parkhurst MR; Shulman EP; Tupesis JP; Custer M; Touloukian CE; Robbins PF; Yafal AG; Greenhalgh P; Sutmuller RP; Offringa R; Rosenberg SA; Restifo NP
Surgery Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
Cancer research (UNITED STATES) Jun 1 1999, 59 (11) p2536-40, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To study the induction of anti-"self" CD8+ T-cell reactivity against the tumor antigen **gp100** , we used a mouse transgenic for a chimeric HLA-A*0201/H-2 Kb molecule (A2/Kb). We immunized the mice with a recombinant **vaccinia** virus encoding a form of **gp100** that had been modified at position 210 (from a threonine to a methionine) to increase epitope binding to the restricting class I molecule. Immunogens containing the "anchor-fixed" modification elicited anti-self CD8+ T cells specific for the wild-type **gp100** (209-217) peptide pulsed onto target cells. More important, these cells specifically recognized the naturally presented epitope on the surface of an A2/Kb-expressing murine melanoma, B16. These data indicate that anchor-fixing epitopes could enhance the function of recombinant virus-based immunogens.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10121069 99179001 PMID: 10077623
Vaccination with a recombinant vaccinia virus encoding a "self" antigen induces autoimmune vitiligo and tumor cell destruction in mice: requirement for CD4(+) T lymphocytes.
Overwijk WW; Lee DS; Surman DR; Irvine KR; Touloukian CE; Chan CC; Carroll MW; Moss B; Rosenberg SA; Restifo NP
Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 16 1999, 96 (6) p2982-7, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Many human and mouse tumor antigens are normal, nonmutated tissue differentiation antigens. Consequently, immunization with these "self" antigens could induce autoimmunity. When we tried to induce immune responses to five mouse melanocyte differentiation antigens, **gp100** , MART-1, tyrosinase, and tyrosinase-related proteins (TRP) 1 and TRP-2, we observed striking depigmentation and melanocyte destruction only in the skin of mice inoculated with a **vaccinia** virus encoding mouse TRP-1. These

mice rejected a lethal challenge of B16 melanoma, indicating the immune response against TRP-1 could destroy both normal and malignant melanocytes. Cytotoxic T lymphocytes specific for TRP-1 could not be detected in depigmented mice, but high titers of IgG anti-TRP-1 antibodies were present. Experiments with knockout mice revealed an absolute dependence on major histocompatibility complex class II, but not major histocompatibility complex class I, for the induction of both vitiligo and tumor protection. Together, these results suggest that the deliberate induction of self-reactivity using a recombinant viral vector can lead to tumor destruction, and that in this model, CD4(+) T lymphocytes are an integral part of this process. Vaccine strategies targeting tissue differentiation antigens may be valuable in cancers arising from nonessential cells and organs such as melanocytes, prostate, testis, breast, and ovary.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09822647 98355607 PMID: 9692858

Generation of polyclonal rabbit antisera to mouse melanoma associated antigens using gene gun immunization.

Surman DR; Irvine KR; Shulman EP; Allweis TM; Rosenberg SA; Restifo NP

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

Journal of immunological methods (NETHERLANDS) May 1 1998, 214 (1-2) p51-62, ISSN 0022-1759 Journal Code: IFE

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Lymphocytes from patients with melanoma have been used to clone melanoma associated antigens which are, for the most part, nonmutated melanocyte tissue differentiation antigens. To establish a mouse model for the use of these 'self' antigens as targets for anti-tumor immune responses, we have employed the mouse homologues of the human melanoma antigens Tyrosinase, Tyrosinase Related Protein-1 (TRP-1), **gp100** , and MART-1. We sought to generate antisera against these proteins for use in the construction of experimental recombinant and synthetic anti-cancer vaccines, and for use in biologic studies. Using genes cloned from the B16 mouse melanoma or from murine melanocytes, we immunized rabbits with plasmid DNAs coated onto microscopic gold beads that were then delivered using a hand-held, helium-driven 'gene gun'. This strategy enabled us to generate polyclonal rabbit sera containing antibodies that specifically recognized each antigen, as measured by immunostaining of **vaccinia** virus infected cells. The sera that we generated specifically for TRP-1, **gp100** , and MART-1 recognized extracts of the spontaneous murine melanoma, B16. The identities of the recognized proteins was confirmed by Western blot analysis. The titers and specificities of these antisera were determined using ELISA. Interestingly, serum samples generated against murine MART-1 and **gp100** developed antibodies that were cross-reactive with the corresponding human homologues. Recognition of human **gp100** and murine Tyrosinase appeared to be dependent upon conformational epitopes since specificity was lost upon denaturation of the antigens. These antisera may be useful in the detection, purification and characterization of the mouse homologues of recently cloned human tumor associated antigens and may enable the establishment of an animal model of the immune consequences of vaccination against 'self antigens.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09817221 98336214 PMID: 9670040

gp100/pmel 17 is a murine tumor rejection antigen: induction of "self"-reactive, tumoricidal T cells using high-affinity, altered peptide ligand.

Overwijk WW; Tsung A; Irvine KR; Parkhurst MR; Goletz TJ; Tsung K; Carroll MW; Liu C; Moss B; Rosenberg SA; Restifo NP

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

Journal of experimental medicine (UNITED STATES) Jul 20 1998, 188 (2) p277-86, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Many tumor-associated antigens are nonmutated, poorly immunogenic tissue differentiation antigens. Their weak immunogenicity may be due to "self"-tolerance. To induce autoreactive T cells, we studied immune responses to **gp100** /pmel 17, an antigen naturally expressed by both normal melanocytes and melanoma cells. Although a recombinant **vaccinia** virus (rVV) encoding the mouse homologue of **gp100** was nonimmunogenic, immunization of normal C57BL/6 mice with the rVV encoding the human **gp100** elicited a specific CD8(+) T cell response. These lymphocytes were cross-reactive with mgp100 in vitro and treated established B16 melanoma upon adoptive transfer. To understand the mechanism of the greater immunogenicity of the human version of **gp100** , we characterized a 9-amino acid (AA) epitope, restricted by H-2Db, that was recognized by the T cells. The ability to induce specific T cells with human but not mouse **gp100** resulted from differences within the major histocompatibility complex (MHC) class I-restricted epitope and not from differences elsewhere in the molecule, as was evidenced by experiments in which mice were immunized with rVV containing minigenes encoding these epitopes. Although the human (hgp10025-33) and mouse (mgp10025-33) epitopes were homologous, differences in the three NH2-terminal AAs resulted in a 2-log increase in the ability of the human peptide to stabilize "empty" Db on RMA-S cells and a 3-log increase in its ability to trigger interferon gamma release by T cells. Thus, the fortuitous existence of a peptide homologue with significantly greater avidity for MHC class I resulted in the generation of self-reactive T cells. High-affinity, altered peptide ligands might be useful in the rational design of recombinant and synthetic vaccines that target tissue differentiation antigens expressed by tumors.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09320756 97256079 PMID: 9101410

Cloning and characterization of the genes encoding the murine homologues of the human melanoma antigens MART1 and gp100.

Zhai Y; Yang JC; Spiess P; Nishimura MI; Overwijk WW; Roberts B; Restifo NP; Rosenberg SA

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

Journal of immunotherapy (UNITED STATES) Jan 1997, 20 (1) p15-25, Journal Code: CUQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The recent identification of genes encoding melanoma-associated antigens has opened new possibilities for the development of cancer vaccines designed to cause the rejection of established tumors. To develop a syngeneic animal model for evaluating antigen-specific vaccines in cancer therapy, the murine homologues of the human melanoma antigens MART1 and **gp100** , which were specifically recognized by tumor-infiltrating lymphocytes from patients with melanoma, were cloned and sequenced from a murine B16 melanoma cDNA library. The open reading frames of murine MART1 and **gp100** encode proteins of 113- and 626-amino acids with 68.8 and 77% identity to the respective human proteins. Comparison of the DNA sequences of the murine MART1 genes, derived from normal melanocytes, the immortalized nontumorgenic melanocyte line Melan-a and the B16 melanoma, showed all to be identical. Northern and Western blot analyses confirmed that both genes encoded products that were melanocyte lineage proteins. Mice immunized with murine MART1 or **gp100** using recombinant **vaccinia** virus failed to produce any detectable T-cell responses or protective immunity against B16 melanoma. In contrast, immunization of mice with human **gp100** using recombinant adenoviruses elicited T cells specific for hgp100, but these T cells also cross reacted with B16 tumor in vitro and induced significant but weak protection against B16 challenge. Immunization with human and mouse **gp100** together [adenovirus type 2 (Ad2)-hgp100 plus

recombinant **vaccinia** virus (rVV)-mgp100], or immunization with human **gp100** (Ad2-hgp100) and boosting with heterologous vector (rVV-hgp100 or rVV-mgp100) or homologous vector (Ad2-hgp100), did not significantly enhance the protective response against B16 melanoma. These results may suggest that immunization with heterologous tumor antigen, rather than self, may be more effective as an immunotherapeutic reagent in designing antigen-specific cancer vaccines.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09068438 97098734 PMID: 8943411

Shared epitopes for HLA-A3-restricted melanoma-reactive human CTL include a naturally processed epitope from Pmel-17/gp100.

Skipper JC; Kittlesen DJ; Hendrickson RC; Deacon DD; Harthun NL; Wagner SN; Hunt DF; Engelhard VH; Slingluff CL

Department of Microbiology, University of Virginia, Charlottesville 22908, USA.

Journal of immunology (UNITED STATES) Dec 1 1996, 157 (11) p5027-33, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI20963, AI, NIAID; CA557653, CA, NCI; GM37537, GM, NIGMS; +

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Human CD8+ CTL recognize peptides bound to class I MHC molecules on the surface of melanoma cells. Several peptides derived from melanocyte lineage-specific proteins have been identified as epitopes for HLA-A2 restricted melanoma-reactive CTL. Because less than half of melanoma patients express HLA-A2, it is important to identify CTL epitopes restricted by other common MHC molecules including HLA-A1 and -A3. We have generated HLA-A3-restricted human CTL that recognize one or more shared melanoma Ags. All of the melanomas recognized by one of these CTL lines express Pmel-17/ **gp100** , and those that fail to express this Ag are not lysed. This CTL line also specifically recognizes the lymphoblastoid line C1R-A3 following infection with a recombinant **vaccinia** encoding the melanocyte lineage-specific protein Pmel-17/ **gp100** . Thus, at least one Pmel-17/ **gp100** peptide is an epitope for this CTL line. We have identified ALLAVGATK (Pmel-17/ **gp100** residues 17-25) as an epitope for this CTL line and have shown that it is naturally processed and presented by HLA-A3 on melanoma cells. A second HLA-A3-restricted melanoma-reactive CTL line recognizes at least one additional shared epitope. These findings suggest that cellular immune responses directed against multiple shared melanoma epitopes exist in the 20 to 25% of melanoma patients who express HLA-A3. In addition, immunotherapy directed against Pmel-17/ **gp100** and other shared melanoma Ags may be useful in a large subset of these patients.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07146278 94025558 PMID: 7692666

Human herpesvirus-6 glycoprotein H and L homologs are components of the gp100 complex and the gH external domain is the target for neutralizing monoclonal antibodies.

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Department of Medicine, University of Cambridge, United Kingdom.

Virology (UNITED STATES) Nov 1993, 197 (1) p12-22, ISSN 0042-6822 Journal Code: XEA

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Previous studies have shown that monoclonal antibody (MAb) 2E4 neutralizes infectivity of human herpesvirus-6 (HHV-6) and also inhibits virus-induced T-lymphocyte syncytia formation. Here we characterize two additional MAbs, 1D3 and 5E7, which have similar properties, and identify the glycoprotein targets. The MAbs could immunoprecipitate and

immunofluorescence glycoprotein from both A and B variant strain groups of HHV-6. In reactions with infected cells the MAbs immunoprecipitated a complex of glycoproteins, the " **gp100** " complex, composed of a major glycoprotein species of 100,000 M(r) and minor components of 80,000 M(r) and 32,000 M(r). We show that the 100,000 M(r) product and most likely the 80,000 M(r) correspond to the HHV-6 homologue of herpes simplex virus-1 (HSV-1) glycoprotein H (gH) while the 32,000 M(r) species corresponds to the glycoprotein L (gL) equivalent. All three MAbs could specifically immunoprecipitate either gH expressed on its own in fibroblasts or a complex of gH and gL co-expressed, but could not immunoprecipitate gL expressed on its own. Consistent with these results, the MAbs could recognize gH in an immunofluorescence assay but not gL. Therefore although the MAbs recognized the complex of glycoproteins, they appeared specific for gH. The HHV-6 glycoproteins were produced in a transient expression system induced by T7- **vaccinia** virus. Immunoprecipitations were carried out in comparisons with an "epitope-tagged" gH, a recombinant glycoprotein designed to contain at the N-terminus the linear epitope for MAb LP14, raised originally against HSV-1 glycoprotein gD. The epitope-tagged gH was also used as a positive control in determining the domain of HHV-6 gH to which MAbs 2E4, 1D3 and 5E7 were directed. Two gH deletions were constructed, one deleting sequences which may serve as a transmembrane and cytoplasmic anchor domains, the second deleting also part of the external domain. MAb LP14 could immunoprecipitate both HHV-6 gH deletions but the **gp100** MAbs recognized only the full-length product or the intact external domain minus the transmembrane and cytoplasmic domains. This indicated the epitopes for these MAbs are contained in the external domain of gH, consistent with the MAbs action in neutralization of virion infectivity and inhibition of virus to cell spread by T-lymphocyte fusion.

3/3,AB/10 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05378071 Genuine Article#: VU501 Number of References: 43
Title: SHAVED EPITOPES FOR HLA-A3-RESTRICTED MELANOMA-REACTIVE HUMAN CTL INCLUDE A NATURALLY PROCESSED EPITOPE FROM PMEL-17/GP100 (Abstract Available)
Author(s): SKIPPER JCA; KITTLESEN DJ; HENDRICKSON RC; DEACON DD; HARTHUN NL ; WAGNER SN; HUNT DF; ENGELHARD VH; SLINGLUFF CL
Corporate Source: UNIV VIRGINIA,DEPT SURG,BOX 181/CHARLOTTESVILLE//VA/22908 ; UNIV VIRGINIA,DEPT SURG/CHARLOTTESVILLE//VA/22908; UNIV VIRGINIA,DEPT MICROBIOL/CHARLOTTESVILLE//VA/22908; UNIV VIRGINIA,BEIRNE CARTER CTR IMMUNOL RES/CHARLOTTESVILLE//VA/22908; UNIV VIRGINIA,DEPT CHEM/CHARLOTTESVILLE//VA/22908; UNIV VIRGINIA,DEPT PATHOL/CHARLOTTESVILLE//VA/22908; UNIV ESSEN GESAMTHSCH,SCH MED,DEPT DERMATOL/ESSEN//GERMANY/
Journal: JOURNAL OF IMMUNOLOGY, 1996, V157, N11 (DEC 1), P5027-5033
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Abstract: Human CD8(+) CTL recognize peptides bound to class I MHC molecules on the surface of melanoma cells. Several peptides derived from melanocyte lineage-specific proteins have been identified as epitopes for HLA-A2 restricted melanoma-reactive CTL. Because less than half of melanoma patients express HLA-A2, it is important to identify CTL epitopes restricted by other common MHC molecules including HLA-A1 and -A3, We have generated HLA-A3-restricted human CTL that recognize one or more shared melanoma Ags. All of the melanomas recognized by one of these CTL lines express Pmel-17/ **gp100** , and those that fail to express this Ag are not lysed, This CTL line also specifically recognizes the lymphoblastoid line C1R-A3 following infection with a recombinant **vaccinia** encoding the melanocyte lineage-specific protein Pmel-17/ **gp100** , Thus, at least one Pmel-17/ **gp100** peptide is an epitope for this CTL line, We have identified ALLAVGATK (Pmel-17/ **gp100** residues 17-25) as an epitope for this CTL line and have shown that it is naturally processed and presented by HLA-A3 on melanoma cells, A second HLA-A3-restricted melanoma-reactive CTL line recognizes at least one additional shared epitope. These findings suggest that cellular immune responses directed against multiple shared melanoma epitopes

Murine dendritic **cells** transfected **with** gp100 **elicit antigen specific, MHC restricted antitumor immunity.**

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JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p84 March, 1998
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English

6/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07181774 93049181 PMID: 1385114

The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity.

Hollenbaugh D; Grosmaire LS; Kullas CD; Chalupny NJ; Braesch-Andersen S; Noelle RJ; Stamenkovic I; Ledbetter JA; Aruffo A

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.

EMBO journal (ENGLAND) Dec 1992, 11 (12) p4313-21, ISSN 0261-4189 Journal Code: EMB

Contract/Grant No.: AI26296, AI, NIAID; GM43257, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Signals delivered to B cells via CD40 can synergize with those provided by other B cell surface receptors to induce B cell proliferation and antibody class switching as well as modulate cytokine production and cell adhesion. Recently, it has been shown that the ligand for CD40 is a cell surface protein of approximately 39 kDa expressed by activated T cells, gp39. Here we report on the isolation and characterization of a **cDNA** clone encoding human gp39, a type II membrane protein with homology to TNF, and the construction and characterization of a soluble recombinant form of gp39. COS cell transfectants expressing gp39 synergized with either anti-CD20 mAb or PMA to drive strong B cell proliferation and alone were able to drive B cells to proliferate weakly. In all cases the B cell proliferation induced by gp39-expressing COS cells was reduced to background levels by the addition of **soluble CD40** . Unlike gp39-expressing COS cells, recombinant soluble gp39 was not mitogenic alone and required co-stimulation to drive B cell proliferation. These results suggest that B cells require a second signal besides gp39-CD40 to drive proliferation and that soluble gp39 alone in a non-membrane bound form is able to provide co-stimulatory signals to B cells.

355738 99446899 PMID: 10519410

Potent activity of soluble **B7 -IgG fusion proteins in therapy of established** tumors **and as vaccine adjuvant.**

Sturmhoefel K; Lee K; Gray GS; Thomas J; Zollner R; O'Toole M; Swiniarski H; Dorner A; Wolf SF

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Cancer research (UNITED STATES) Oct 1 1999, 59 (19) p4964-72, ISSN 0008-5472 Journal Code: CNF

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Fusion proteins consisting of the extracellular region of murine **B7** .1 or **B7** .2 and the Fc portion of murine IgG2a (**B7** -IgG) were evaluated for their ability to promote antitumor responses. Therapeutic administration of **soluble B7** -IgG in mice with established **tumors** induced complete regression of the **tumor** and increased the survival of mice. In three models, MethA, P815, and MB49, mice with 7-day-old established **tumors** were cured with two to three treatment cycles of **B7** -IgG, given twice a week. Even in mice with an established B16/F10 **tumor** (a poorly immunogenic melanoma), therapeutic treatment with **B7** -IgG alone slowed **tumor** growth and increased survival significantly. Still stronger antitumor activity was achieved when **B7** -IgG was used as a vaccine adjuvant mixed with irradiated **tumor** cells. In 80% of mice with 7-day-old B16 **tumors** , **tumors** regressed completely, and mice survived for at least 80 days. In all **tumor** models, **B7** .1-IgG and **B7** .2-IgG had similar antitumor activity. **B7** -IgG-mediated **tumor** rejection was dependent on T cells, specifically CD8 cells, as demonstrated by the failure of **B7** -IgG to induce **tumor** regression in severe combined immunodeficient or CD8-depleted mice. In addition, mice that were cured of an established **tumor** were protected against a rechallenge with the same **tumor** for at least 4 months, suggesting the generation of memory responses.

The mode of presentation and route of administration are critical for the induction of immune responses to p53 and antitumor immunity.

Hurpin C; Rotarioa C; Bisceglia H; Chevalier M; Tartaglia J; Erdile L
Pasteur Merieux Connaught, Marcy L'Etoile, France.

Vaccine (ENGLAND) Jan-Feb 1998, 16 (2-3) p208-15, ISSN 0264-410X
Journal Code: X60
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We have examined the immune response to full-length wild-type human p53 presented by a recombinant canarypox vector (**ALVAC**) and by plasmid DNA. For the **ALVAC** recombinant, intravenous, but not subcutaneous, intramuscular or intradermal administration, induced CD8+ CTLs that lysed tumor cells transfected with human mutant p53. **Intrasplenic** administration also induced CTLs. Biodistribution studies showed that intravenously injected **ALVAC** localized primarily in the lung, liver and spleen, whereas intramuscularly injected virus remained predominantly at the injection site. Intradermal and intramuscular immunization with naked plasmid DNA encoding human wild-type p53 also induced a specific CTL response. DNA immunization induced complete protection against challenge with a mouse embryo fibroblast transfected with human mutant p53 and partial, but significant, protection against a transfected mastocytoma. The **ALVAC** recombinant induced partial protection in both models. These results suggest that recombinant **ALVAC** and DNA might be interesting presentation platforms for p53 to be tested in clinical studies.

Gene transfer to the thymus. A means of abrogating the immune response to recombinant adenovirus.

DeMatteo RP; Raper SE; Ahn M; Fisher KJ; Burke C; Radu A; Widera G; Claytor BR; Barker CF; Markmann JF

Harrison Department of Surgical Research, University of Pennsylvania, Philadelphia, USA.

Annals of surgery (UNITED STATES) Sep 1995, 222 (3) p229-39; discussion 239-42, ISSN 0003-4932 Journal Code: 67S

Contract/Grant No.: CF P30D47757-01, PHS; DK 26007, DK, NIDDK; F32 DK09125-01, DK, NIDDK

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

@ R01, A55 1

OBJECTIVE: The authors investigated whether adenoviral gene transfer to the thymus could be accomplished in vivo and whether immunologic unresponsiveness to recombinant adenovirus could be induced by intrathymic inoculation. SUMMARY BACKGROUND DATA: A major barrier to the clinical application of adenovirus-mediated gene therapy for diseases requiring long-lasting gene expression is the immunogenicity of adenoviral vectors, which limits the duration of its effects. In other experimental models, intrathymic inoculation of foreign proteins or cells has proven to be an effective means to induce immunologic tolerance. METHODS: The efficiency of gene transfer to the mouse thymus after direct inoculation of recombinant adenovirus was compared with that of several other vectors. Animals inoculated with adenovirus-infected pancreatic islets into the thymus were tested for unresponsiveness to the virus with a subsequent challenge of adenovirus administered into the liver by intravenous injection. RESULTS: Adenovirus accomplished highly efficient gene transfer to the thymus, unlike plasmid DNA, DNA-liposome complexes, retrovirus, and adeno-associated virus. Adenoviral transgene expression was transient in the thymus of immunocompetent mice but persistent in CD8+ T-cell-deficient and severe combined immunodeficiency (SCID) mice, implicating the role of cytotoxic T lymphocytes in viral clearance. Intrathymic transplantation of syngeneic pancreatic islet cells infected with adenovirus impaired the normal antiviral cytotoxic T-lymphocyte response and prolonged hepatic transgene expression after an intravenous challenge with adenovirus. CONCLUSIONS: Recombinant adenovirus accomplishes highly efficient gene transfer to the thymus in vivo. Intrathymic inoculation of adenovirus-infected islets can be used to induce immunologic unresponsiveness to the adenoviral vector and, potentially, to other proteins that it might be engineered to encode.

Evidence for local and systemic activation of immune cells by peritumoral injections of interleukin 2 in patients with advanced squamous cell carcinoma of the head and neck.

Whiteside TL; Letessier E; Hirabayashi H; Vitolo D; Bryant J; Barnes L; Snyderman C; Johnson JT; Myers E; Herberman RB; et al

Department of Pathology, University of Pittsburgh School of Medicine, Pennsylvania 15213.

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Languages: ENGLISH

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Interleukin 2 (IL2) was injected peritumorally and **intranodally** in 36 patients with unresectable squamous cell carcinoma of the head and neck enrolled in an Eastern Cooperative Oncology Group-sponsored phase Ib trial (EST P-Z388). Groups of 6 patients received escalating doses(200, 2 x 10(3), 2 x 10(4), 2 x 10(5), 2 x 10(6), and 4 x 10(6) units) of IL2 daily 5 times/week for 2 weeks. Tumor biopsies were obtained before and after IL2 therapy. Tumor tissue was provided for histology, and the remaining fresh tissue was divided for snap-freezing in -75 degrees C and for separation of tumor-infiltrating lymphocytes (TIL) and tumor cells. Immunophenotyping of TIL performed on cryostat sections of paired pre- and post-IL2 biopsy tissues showed increases after IL2 therapy in the number of T-cells ($P = 0.005$), natural killer (NK; CD16+) cells ($P = 0.0001$), CD25+ cells ($P = 0.004$), and HLA-DR+ cells ($P = 0.001$) accumulating in the tumor stroma. In the tumor parenchyma, NK cells ($P = 0.0001$) and HLA-DR+ cells ($P = 0.003$) were increased after IL2 therapy. The T:NK cell ratios in the tumor stroma and parenchyma were decreased after therapy, suggesting selective accumulation of NK cells. By flow cytometry, TIL recovered from post-IL2 biopsy tissues were enriched ($P < 0.05$) in CD3-CD56+ (NK) cells. In situ hybridization with [35S] cDNA probes for cytokines and IL2 receptors indicated that the numbers of cells expressing mRNA for IL2, tumor necrosis factor alpha, IL1-beta, gamma-interferon, transforming growth factor beta, and IL2 receptor p55 or p70 were increased in post-IL2 biopsy tissues as compared to pre-IL2 tissues. Cytolytic activity of TIL isolated from post-IL2 tissues was also increased, as determined in 4-h 51Cr release assays against K562 targets (12 +/- 3 mean lytic units/10(7) cells +/- SEM pre-IL2 versus 46 +/- 13 post-IL2; n = 16) and against autologous tumor (13 +/- 8 versus 68 +/- 26; n = 9). Fresh TIL of one clinical responder showed relatively high levels (195 lytic units) of autotumor cytotoxicity after IL2 therapy versus no activity prior to therapy. In the blood, NK and lymphokine-activated killer cell activity, and percentages of CD3-CD56+ NK cells and of activated (CD25+) T-lymphocytes were increased for all doses of IL2.(ABSTRACT TRUNCATED AT 400 WORDS)

vaccinate patients with metastatic melanoma. The purpose of this study was to evaluate the success of the vaccinations, as determined by the results of enzyme-linked immunospot (ELISPOT) tests of individual immune cells. PATIENTS AND METHODS: The ELISPOT assay was used to measure the immunologic reactivity of peripheral blood lymphocytes from patients with metastatic melanoma before and after vaccination with gp100 peptides mixed with incomplete Freund's adjuvant. The peptides were g209 (ITDQVPFSV), g280 (YLEPGPVTA), modified g209 (g209-2M: IMDQVPFSV) or modified g280 (g280-9V: **YLEPGPVTV**) peptide. The patients' lymphocytes were tested by use of an ELISPOT assay for their ability to secrete interferon gamma with and without 12 days of in vitro sensitization with peptide. RESULTS: Patients were successfully vaccinated by gp100 peptides, as judged by the ELISPOT assays. Restimulation of the patients' lymphocytes in vitro with peptide for 12 days before the ELISPOT assay significantly amplified the immune activity. Increased immune activity after vaccination was specific for the immunizing peptide or its altered form, was major histocompatibility complex restricted, and was apparent against HLA-A2+, gp100+ melanoma cell lines and against T2 cells pulsed with the appropriate synthetic peptides. In general, the frequency of immune T cells was 10 to 100-fold higher in ELISPOT assays against peptide-pulsed T2 cells than against melanoma cell lines. Judged by the ELISPOT assays, vaccination was successful in six of seven patients injected with g209-2M when tested against g209-2M peptide and in five of these seven patients when tested against the native g209 peptide. Vaccination was also successful in five of six patients injected with g209, one of three patients injected with g280-9V, and four of seven patients injected with g280. Even without peptide restimulation in vitro before the ELISPOT assay, the frequency of immune T cells among fresh peripheral blood mononuclear cells tested 3 weeks after a second vaccination with g209-2M peptide was elevated in four of six patients and was about 1/1000 of cells tested against the same peptide pulsed onto T2 cells. DISCUSSION: Gp100 peptides were selected for vaccine development because they are epitopes recognized by tumor-infiltrating lymphocytes that are associated with tumor regression after adoptive immunotherapy in patients with metastatic melanoma. In the present study, most of the patients vaccinated with the gp209-2M peptide in incomplete Freund's adjuvant generated circulating antigen-specific immune T cells that could be detected by restimulation in vitro followed by an ELISPOT assay for individual cells secreting interferon gamma. The immune T cells reacted not only with the HLA-A2 restricted modified peptide but also with the native peptide and with melanoma cells that express gp100 and HLA-A2. Analysis of T-cell responses at the single cell level will be a valuable aid in assessing the effectiveness of melanoma vaccines and in determining optimal vaccine formulations and delivery.

8/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09415536 98021980 PMID: 9377571

Identification of an enhancer agonist cytotoxic T lymphocyte peptide from human carcinoembryonic antigen.

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A vaccination strategy designed to enhance the immunogenicity of self-antigens that are overexpressed in tumor cells is to identify and slightly modify immunodominant epitopes that elicit T-cell responses. The resultant T cells, however, must maintain their ability to recognize the native configuration of the peptide-MHC interaction on the tumor cell target. We used a strategy to enhance the immunogenicity of a human CTL epitope directed against a human self-antigen, which involved the modification of individual amino acid residues predicted to interact with the T-cell receptor; this strategy, moreover, required no prior knowledge of these actual specific interactions. Single amino acid substitutions were

introduced to the CAP1 peptide (YLSGANLNL), an immunogenic HLA-A2+-binding peptide derived from human carcinoembryonic antigen (CEA). In this study, four amino acid residues that were predicted to potentially interact with the T-cell receptor of CAP1-specific CTLs were systematically replaced. Analogues were tested for binding to HLA-A2 and for recognition by an established CTL line directed against CAP1. This line was obtained from peripheral blood mononuclear cells from an HLA-A2+ individual vaccinated with a vaccinia-CEA recombinant. An analogue peptide was identified that was capable of sensitizing CAP1-specific CTLs 10(2)-10(3) times more efficiently than the native CAP1 peptide. This enhanced recognition was shown not to be due to better binding to HLA-A2. Therefore, the analogue CAP1-6D (**YLSGADLNL** , Asn at position 6 replaced by Asp) meets the criteria of a CTL enhancer agonist peptide. Both the CAP1-6D and the native CAP1 peptide were compared for the ability to generate specific CTL lines in vitro from unimmunized apparently healthy HLA-A2+ donors. Whereas CAP1 failed to generate CTLs from normal peripheral blood mononuclear cells, the agonist peptide was able to generate CD8+ CTL lines that recognized both the agonist and the native CAP1 sequence. Most importantly, these CTLs were capable of lysing human tumor cells endogenously expressing CEA. The use of enhancer agonist CTL peptides may thus represent a new efficient direction for immunotherapy protocols.

8/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09002735 96438634 PMID: 8840994
Immunization against epitopes in the human melanoma antigen gp100 following patient immunization with synthetic peptides.
Salgaller ML; Marincola FM; Cormier JN; Rosenberg SA
Surgery Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
Cancer research (UNITED STATES) Oct 15 1996, 56 (20) p4749-57, ISSN 0008-5472 Journal Code: CNF
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Document type: Clinical Trial; Clinical Trial, Phase I; Controlled Clinical Trial; Journal Article
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gp100 is a melanocytic lineage-specific antigen recognized by tumor-infiltrating lymphocytes, the adoptive transfer of which is associated with tumor regression in melanoma patients. In this study, peripheral blood mononuclear cells (PBMCs) were harvested from HLA-A2+ melanoma patients before and after immunization with G9-209 (ITDQVPFSY), G9-280 (YLEPGPVTA), or G9-154 (KTWGQYWQV) peptides in Incomplete Freund's Adjuvant and were tested for the ability to be sensitized in vitro using PBMCs pulsed with the native peptides. In addition, PBMCs from patients receiving the G9-209 or G9-280 peptide were stimulated in vitro with peptides modified at anchor residues to enhance binding to HLA-A2: G9-209/2M (IMDQVPFSY) or G9-280-9V (**YLEPGPVTV**). In patients immunized with G9-209, a single in vitro restimulation with G9-209/2M resulted in the generation of specific antipeptide lymphocytes from seven of seven postimmune PBMCs and only three of seven preimmune PBMCs. In patients immunized with G9-280, a single in vitro restimulation with G9-280/9V resulted in the generation of specific antipeptide lymphocytes from five of six postimmune PBMCs and four of six preimmune PBMCs. In almost all cases, CTLs raised against modified epitopes were capable of recognizing targets displaying the native nonamers. Several anti-G9-209 and anti-G9-209/2M CTLs also demonstrated specific lysis of, and specific IFN-gamma release in response to, gp100+-established cell lines. Thus, using peptides modified to enhance immunogenicity for in vitro stimulation improved the sensitivity of immune monitoring of patients immunized with synthetic peptides. These results demonstrate that immunization with a peptide derived from a tumor-associated protein such as gp100 can provoke a measurable antitumor immune response in cancer patients.
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with the **CEA** immunodominant CTL epitope carcinoembryonic antigen peptide-1 and interleukin 2 and quantitated using CTL precursor frequency analysis. In seven of nine patients evaluated, statistically significant increases in CTL precursors specific for **CEA** were observed in PBMCs after vaccination, compared with before vaccination. CONCLUSION: These studies constitute the first phase I trial of an avipox recombinant in cancer patients. The recombinant vaccine **ALVAC** - **CEA** seems to be safe and has been demonstrated to elicit **CEA** -specific CTL responses. These studies thus form the basis for the further clinical exploration of the **ALVAC** - **CEA** recombinant vaccine in phase I/II studies in protocols designed to enhance the generation of human T-cell responses to **CEA** .

6/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09506857 96124869 PMID: 8548758
MAGE-1-specific precursor cytotoxic T-lymphocytes present among tumor-infiltrating lymphocytes from a patient with breast cancer: characterization and antigen-specific activation.
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Cancer research (UNITED STATES) Jan 1 1996, 56 (1) p16-20, ISSN 0008-5472 Journal Code: CNF
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Document type: Journal Article
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A potential target for development of tumor-specific immunotherapeutic strategies is the **MAGE** -1 gene. We have utilized a recently developed recombinant canarypox (**ALVAC**) virus vector containing the **MAGE** -1 gene (vCP235) to activate CTLs from a breast cancer patient bearing a **MAGE** -1+ tumor. Tumor-infiltrating lymphocytes (TILs) obtained from the tumor of a patient were stimulated in vitro with irradiated autologous peripheral blood mononuclear cells acutely infected with the vCP235 construct. These TILs preferentially expanded approximately 6-fold over a 16-day culture period and specifically recognized an allogeneic transformed B-cell line acutely infected with a vaccinia- **MAGE** -1 recombinant targeting vector (vP1188) in the context of HLA-A2 and/or B7. TCR V beta analysis of in vitro expanded T cells by a quantitative multiprobe RNase protection assay revealed preferential expansion of TCR V beta 6.3 and V beta 6.4. In addition, homologous T-cell receptor beta CDR3 joining sequences were found in the in vitro stimulated cultures. These results suggest that tumor antigen-specific, MHC-restricted CTLs may be derived from precursor CTLs present in TILs obtained from patients with **MAGE** -1+ tumors by in vitro stimulation with recombinant avipox **MAGE** -1 virus-infected autologous cells. Collectively, these findings provide a rationale for tumor-associated antigen-based immunization as a means of activating precursor CTLs residing in patients with tumors expressing defined tumor-associated antigens such as **MAGE** -1.

6/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09369539 97321777 PMID: 9178479
Diversified prime and boost protocols using recombinant vaccinia virus and recombinant non-replicating avian pox virus to enhance T-cell immunity and antitumor responses.
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Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
Vaccine (ENGLAND) Apr-May 1997, 15 (6-7) p759-68, ISSN 0264-410X Journal Code: X60
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A. Donis

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Recombinant vaccinia viruses containing tumor associated genes represent an attractive vector to induce immune responses to weak immunogens in cancer immunotherapy protocols. The property of intense immunogenicity of vaccinia proteins, however, also serves to limit the number of inoculations of recombinant vaccinia viruses. Host immune responses to the first immunization have been shown to limit the replication of subsequent vaccinations and thus reduce effectiveness of boost inoculations. The use of recombinant avian pox viruses (avipox) such as the canarypox (**ALVAC**) or fowlpox are potential candidates for immunization protocols in that they can infect mammalian cells and express the inserted transgene, but do not replicate in mammalian cells. We report here the construction and characterization of a canarypox (**ALVAC**) recombinant expressing the human carcinoembryonic antigen (**CEA**) gene (designated **ALVAC - CEA**). Antibody, lymphoproliferative and cytolytic T-cell responses as well as tumor inhibition were shown to be elicited by the **ALVAC - CEA** recombinant in a murine model. The utilization of a diversified immunization scheme using a recombinant vaccinia virus followed by recombinant avian pox virus was shown to be far superior than the use of either one alone in eliciting **CEA** -specific T-cell responses. Experiments were conducted to determine if the use of a diversified immunization scheme using a recombinant vaccinia virus (rV- **CEA**) and **ALVAC - CEA** would be superior to the use of either one alone in eliciting **CEA** -specific T-cell responses. When mice were immunized with rV- **CEA** and then **ALVAC - CEA** . **CEA** -specific T-cell responses were at least four times greater, and for superior to those achieved with three immunizations of **ALVAC - CEA** . Multiple boosts of **ALVAC - CEA** following rV- **CEA** immunization further potentiated anti-tumor effects and **CEA** specific T-cell responses. These studies demonstrate the proof of concept of the advantage of diversified immunization protocols employing both recombinant vaccinia and recombinant avipox vectors.

6/3,AB/5 (Item 1 from file: 159)

01590619 99701693

Prliminary Results of ALVAC - CEA **-B7 Phase I Vaccine Trial in Patients with Metastatic** CEA **-expressing Tumors. (Meeting abstract).**

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Proc Annu Meet Am Soc Clin Oncol; 18 1999
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Document Type: MEETING ABSTRACTS
Record type: Completed

ALVAC is a canarypox virus capable of non-replicative infection of mammalian cells and can present foreign antigens without inducing a neutralizing antibody response. Carcinoembryonic antigen (**CEA**) is one of the best-characterized and widely-expressed tumor-associated antigens. Recent studies have found evidence that recombinant viral vectors expressing human **CEA** can activate **CEA** -specific T-cells. Activation of T-cells depends on recognition of the peptide-MHC complex by the T-cell receptor in association with a second signal delivered by co-stimulatory molecules, such as B7.1. In order to improve the effectiveness of tumor vaccines for cancer therapy a recombinant **ALVAC - CEA** -B7.1 vaccine was generated and tested in a dose-escalation Phase I clinical trial. The trial objectives included determination of the optimum tolerated dose, toxicity, clinical response, and development of **CEA** -specific immunity. 18 patients were enrolled representing 13 colorectal, 3 non-small cell lung, 1 gastric, and 1 pancreatic carcinoma. Cohorts of six patients received 3 doses of **ALVAC - CEA** -B7.1 vaccine (4.5 x 10e6, 4.5 x 10e7, or 4.5 x 10e8 Plaque-Forming Units) by monthly intramuscular injection. The mean age of participants was 59 years and included 8 females and 10 males. Patients tolerated up to 4.5[times]10e8 PFU of vaccine without any significant toxicity. Currently 17 patients are evaluable for response and we observed 2 patients with stable disease for over 8 months and 1 mixed response in a pancreatic cancer patient who is alive and well 12 months after diagnosis.